**REMARKS**

Claim 28 is pending in the instant application. Claim 28 has been rejected. Claim 28 has been amended. Reconsideration is respectfully requested in light of these amendments and the following remarks.

**I. Restriction Requirement**

The Restriction Requirement requiring election of the species K93 has been deemed proper and made Final. Applicant has amended claim 28 to reflect the election.

**II. Rejection of Claims Under 35 U.S.C. 112, First Paragraph**

Claim 28 has been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The Examiner acknowledges that the specification is enabling for methods to modulate the chronic actions of morphine as an opium alkaloid, but suggests that the specification does not reasonably provide enablement for the prevention or reversal of chronic actions by the administration of calcium calmodulin dependent protein kinase II inhibitors. Applicant respectfully traverses this rejection.

In an earnest effort to advance the prosecution and facilitate allowance of the claim, Applicant has amended claim 28

to recite the language that is suggested by the Examiner to be enabled by the disclosure of the instant invention. Accordingly, the claim as amended meets the requirement of 35 U.S.C. 112, first paragraph and withdrawal of this rejection is respectfully requested.

**III. Rejection of Claims Under 35 U.S.C. § 102**

Claim 28 has been rejection under 35 U.S.C. § 102(b) as being anticipated by Fan et al. (1999). The Examiner suggests that this reference discloses the administration of K93 in a saline vehicle by micro-injection in rats. The Examiner suggests that the route of administration is intra-hippocampal injection and that the injection was done before morphine treatment in order to inhibit calcium calmodulin dependent protein kinase II activity. Applicant respectfully traverses this rejection.

At the outset, in an earnest effort to advance the prosecution of this case, Applicant has amended the claim to recite that K93 is administered intrathecally. Support for this amendment can be found throughout the specification as filed where it is shown that *in vivo* administration of K93 intrathecally reduced tolerance and dependence to an opium alkaloid. Applicant refers the Examiner to any of the examples of the application where rats are administered K93.

Fan et al. (1999) was a study in rats which was designed to examine whether inhibition of hippocampal calcium calmodulin dependent protein kinase II prevents morphine tolerance and dependence. Data in the reference show that administration of either KN-62 or K93 to rats by the intra-hippocampal route led to attenuation of tolerance to the analgesic effects of morphine. The reference also teaches that administration of calcium calmodulin dependent protein kinase II antisense oligonucleotides decreased calcium calmodulin dependent protein kinase II expression and produced the same result, linking the activity of the drugs administered to inhibition of the activity of the enzyme. However, data provided in the paper also show that injection of either drug into the striatal region of rat brain failed to affect morphine tolerance, linking the effect of K93 to a specific route of administration (intra-hippocampal injection). Nowhere does this reference teach or suggest that injection of K93 by any route other than intra-hippocampally would lead to an effect to reduce morphine tolerance and dependence.

Contrary to the reference of Fan et al. (1999), the instant specification teaches that administration of K93 intrathecally is effective in reducing the chronic actions of an opium alkaloid, wherein chronic actions are defined as tolerance and dependence actions. Intrathecal administration is an entirely different

route of administration than intra-hippocampal injection. When a drug is administered intrathecally it is introduced into the space around the spinal cord and as such is available to circulate throughout the spinal column, and even into the brain (Marieb, E.N. 1992. Human Anatomy and Physiology, 2nd edition. Benjamin/Cummings Publishing: Redwood City, CA, page 404). Therefore, this route of administration exposes areas of the nervous system more broadly and is not a restricted route of administration (intra-hippocampal) as is taught by Fan et al. Further, since Fan et al. disclose that striatal injection of K93 failed to have an effect, this reference does not teach or suggest that any route other than direct intra-hippocampal injection is effective.

MPEP 2131 states that in order to anticipate an invention the cited reference must teach each and every limitation of the claims. As discussed above, the cited reference fails to teach the limitations of the claims as amended. Accordingly, the reference cannot anticipate the instant invention and withdrawal of this rejection is respectfully requested.

## IV. Conclusion

Applicant believes that the foregoing comprises a full and complete response to the Office Action of record. Accordingly,

favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

Jane Massey Licata
Registration No. 32,357

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Licata & Tyrrell P.C.
66 E. Main Street
Marlton, NJ 08053

856-810-1515